The Examiner has made the restriction requirement final. Applicants maintain their election of Group I, claims 1-6 and 8-9, but do so without traverse.

Claims 1-9 are pending. Claim 7 is withdrawn as being directed to a non-elected invention. Claim 1 is amended to more particularly point out and distinctly claim what Applicants regard as their invention. Applicants claim a method for treating TNF-mediated inflammatory diseases which comprises administering to a mammal in need thereof a therapeutically effective amount of a TNF antagonist selected from the group consisting of a TNF receptor, a TNF binding protein and a chimeric antibody comprising a TNF receptor and the constant domain of an immunoglobulin molecule.

Rejection Under §112, First Paragraph

The specification is objected to under 35 U.S.C. §112, first paragraph, as allegedly failing to describe and teach how to make and/or use the instant invention. Claims 1-6 and 8-9 stand rejected under the §112, first paragraph for the same reasons. The Examiner asserts that Applicants have not defined the phrase "sufficient homology", and that the ordinary artisan would be required to resort to undue experimentation to determine whether proteins are "substantially homologous."

Applicants disagree with the rejection for the following reasons. At the outset, Applicants note that neither of the phrases "sufficient homology" nor "substantially homologous" have been used in the instant application or claims. As such, specific definitions thereof will not be found in the application. However, Applicants have specifically defined the following terms which provide the ordinary artisan with sufficient description of the invention: "amino acids sequences substantially similar" (see page 3, line 4 and page 6, lines 26-38); "analogs or subunits" (see page 3, line 12 and page 7, line 1 to page 8, line 11); "bioequivalent protein and amino acid analogs" (see page 3, lines 15-16 and page 6, lines 16-38); "equivalent soluble TNFRs" (see page 3, line 20); "derivatives of TNFR" (see page 5, line 14); and "functional mutant analogs of mammalian TNFR" (see page 6, lines 2-15 and page 7, line 27 to page 8, line 11). The definitions themselves are not repeated here due to their length, and the reference to page and line numbers is made for the convenience of the Examiner. Also included in each of the definitions noted above is a detailed description of how to make and use such polypeptides. All techniques referenced in the descriptions are well known and the ordinary artisan would not find it necessary to resort to "undue experimentation" in order to make any of the defined proteins. Withdrawal of the objection to the specification is respectfully requested since the specification does provide a description of the invention

Rejection under 35 U.S.C. §101

Claims 1-6 and 8-9 stand rejected under 35 U.S.C. §101 as claiming an invention that is allegedly inoperative and that allegedly lacks utility. The Examiner asserts on page 3 of the Office Action that the data presented in the specification is:

> not accurate enough to really show a reduction in joint diameter. Furthermore, the reduction is not shown to actually improve the condition of the patient. * * * In addition, the data in the Tables A-D does not show that the Fc/TNFR fusion is effective when administered alone.

Applicants respectfully traverse the rejection. Table A on page 20 of the instant application indicates dosage information for various TNF antagonists. It does not show data obtained from clinical experiments. Moreover, contrary to the Examiner's interpretation of the data in Table B on page 21 of the application, there is a significant decrease in histopathology score for the TNF antagonists versus the saline control. Indeed, as shown in Table B and stated in the specification, the diluent-treated control rats scored higher (18.4 ± 4.9), and therefore was less effective, than *any* of the TNF antagonists (mean range of 7.9 ± 5.2 to 13.4 ± 3.6). These results indicate the effectiveness of the TNF antagonists against antigen-induced arthritis.

The Examiner states that "the only apparent effective combination seems to be the combination with the IL-1R." Simply because the combination of IL-1R with TNFR monomer produced a synergistic effect, does not mean that use of the TNFR monomer alone was ineffective. Indeed, TNFR monomer (12.8 ± 3.1) and TNFR:Fc (13.4 ± 3.6) were both more effective than the saline control. Applicants do not understand why the Examiner thinks this data is not clinically significant since the TNFR score of 12.8 is approximately a 30% decrease in score versus the control score of 18.4. Clarification is respectfully requested.

With regard to Table C, the advantage of administering TNFR:Fc to treat collagen-induced arthritis is obvious. The TNF antagonist delayed the onset of the arthritis as compared to the PBS control (21 ± 2 days versus 18∫± 1 day). Similarly, with regard to Table D, administration of 10μg of TNFR:Fc significantly delayed the onset of arthritis as compared to PBS control (27 ± 6 days for TNFR:Fc versus 21 ± 1 day for PBS). As stated in the specification, TNFR:Fc was effective in delaying the onset of CIA when administered over the entire course of the CIA development. Therefore, it is not clear why the Examiner doubts that the TNF antagonist is effective.

The Examiner also states at page 3 of the Office Action that the data of Figures 3 and 4 does not demonstrate "statistically significant" effectiveness of TNFR:Fc as compared to saline. Applicants respectfully disagree. Figures 3 and 4 show the effect of intra-articular administration of recombinant human TNFR:Fc, monomeric TNFR, recombinant murine IL-1R and TNFR monomer combined with rmu IL-1R on antigen-induced arthritis in rats. Since both Figures 3 and 4 show clear and definitive results, applicants do not understand what the Examiner considers to be "statistically significant." Each Figure shows very apparent reduction in the swelling of the joint. A simple statement by the Examiner that the results are not "statistically significant" does not automatically make it so. Certainly one of skill in the art would readily recognize that the claimed TNF antagonists possess the disclosed utility. Withdrawal of the rejection is requested.

Rejection under 35 U.S.C. §101/§112

Claims 1-6 and 8-9 stand rejected under 35 U.S.C. §101 as claiming an invention that allegedly lacks utility. In addition, it is stated in the Office Action at page 3 that the claims are rejected under 35 U.S.C. §112, first paragraph as allegedly "failing to teach how to make and/or use the instant invention."

With regard to the rejection under §112, Applicants note that it is not the purpose of the claims to "teach how to make and/or use the instant invention." According to §112, first paragraph, that purpose is reserved for the specification, which has not been specifically objected to here. The claims are to particularly point out and distinctly claim the subject matter which the Applicants regard as their invention (§112, second paragraph). Therefore, since the statement of the rejection is unclear, Applicants can not respond thereto. The rejection must either be restated or withdrawn.

In the remaining aspect of the §101 rejection, the Examiner alleges that

> the generalization from rats to humans is not realistic absent concrete evidence to the contrary. The anatomical differences between the two mammals would render the extrapolation of rodent data to humans unpredictable.

In an attempt to render support for the Examiner's position, a review article by Bloom was cited. The Examiner referred Applicants to the second column, second paragraph, line 9 wherein it is stated:

> It is noteworthy that in a mouse model of leishmaniasis in which a protective type 1 T cell response was inhibited by type 2 T cells, administration of IFN-γ, known to be critical to protection, was not able to induce a cure.

> cells, administration of IFN-γ, known to be critical to protection, was not able to induce a cure.

The Examiner interpreted this simple statement as somehow indicating that different results with IFN-γ were obtained in mice as compared to humans. Such an interpretation has led to the instant rejection. Nowhere in that referenced paragraph is such a statement made. Indeed, the paragraph simply states that IFN-γ could not cure the mice from *leishmaniasis*. No comparison to IFN-γ effect in humans was made. Indeed leishmaniasis is a different disease, and IFN-γ is a different molecule.

Moreover, the Examiner indicates that rats and humans have certain "anatomical differences" and "different immune systems" that could render the extrapolation of data from rats to humans unpredictable. The Examiner desires "proof" of the conventional use of rats as a model for arthritis. Applicants refer the Examiner to the enclosed article by Trentham, et al., *J. Exp. Med.*, 146:857-868 (1977), wherein approximately 40% of rats injected intradermally with native type II collagen, derived from human, chick or rat cartilage, develop an inflammatory arthritis. Trentham et al. discovered that the characteristics of the arthritis resemble those of rheumatoid arthritis in humans. Trentham et al. state at page 866:

> histopathologic studies show that the primary lesion provoked by type II collagen is a chronic proliferative synovitis. Destruction of articular cartilage and bone appear to be sequelae of synovial inflammation. Mononuclear cells invade and persist in the synovium, suggesting that immune processes may be important in the pathogenesis of disease. These characteristics sufficiently resemble those of rheumatoid arthritis to suggest that this may be an appropriate animal model for the human disease. [emphasis added.]

In view of the Trentham et al. article, it is clear that Applicants methods are art-accepted models of arthritis in humans. Applicants submit that they are entitled to claim a method of treating humans based on the data obtained and disclosed in the specification. Withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. §102

Claims 1-6 and 8-9 stand rejected under 35 U.S.C. §102 as allegedly being anticipated by Brennan et al.

Applicants respectfully disagree with the rejection. It is axiomatic that in order for Applicants' claims to be anticipated under §102, every element of the claimed invention must

Brennan et al. disclose that an anti-TNFα antibody inhibits synovial cell interleukin-1 production in patients with rheumatoid arthritis. However, Applicants' claim 1 recites a Markush group of TNF antagonists, none of which is an anti-TNFα antibody. Therefore, it is clear that every element of the claimed invention is not present in Brennan et al. Withdrawal of the rejection is requested.

Rejection Under 35 U.S.C. §103

Claims 1-6 and 8-9 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Brennan et al. and Harris in view of Smith.

Applicants traverse the rejection simply because Brennan et al. cannot be combined with Harris et al. or Smith et al. since neither Harris et al. nor Smith et al. is available as a prior art reference. Both Harris et al. and Smith et al. were published in May 1990, which is well after Applicants' claimed priority date. Therefore, the Brennan et al. article must stand alone in this rejection. One of the reasons that Brennan et al. do not render Applicants' claims obvious is that Brennan et al. disclose only an anti-TNFα antibody. No claimed TNF antagonists are disclosed or suggested by Brennan et al. Brennan et al. do not suggest or disclose the advantages of using the claimed TNF receptors, TNF binding proteins or even the TNFR:Fc fusions to treat TNF-mediated inflammation. Without such suggestion, Brennan et al. cannot render the claimed invention obvious. Withdrawal of the rejection is requested.

Rejection Under 35 U.S.C. §103

Claims 1-6 and 8-9 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Brennan et al. and Harris in view of Capon and Hoogenboom in further view of Smith.

Applicants respectfully disagree for the same reasons as detailed in response to the previous rejection. Harris et al., Smith et al., and Hoogenboom each have effective dates that are not prior to Applicants' claimed §120 priority date. These documents are therefore not available as prior art against Applicants' invention.

Capon et al., like Brennan et al., do not disclose the use of the claimed TNF antagonists for treating TNF mediated inflammation. Capon et al. simply disclose the construction of a fusion molecule containing *LHR* and the constant domain of an immunoglobulin molecule. There is absolutely no disclosure or suggestion in Capon et al. of constructing a fusion molecule using a *TNF receptor*. Since the disclosure lacking in Capon et al. is not found in Brennan et al., any combination thereof to establish a teaching of a TNFR:Fc is improper. The Examiner correctly states that Capon et al. generically teach that a "ligand-

binding partner" may be used to "moieties that prolong the *in vivo* plasma half life of the ligand-binding partner" (column 4, lines 39-41 of Capon et al.). Such generic teaching is insufficient both alone and when combined with the disclosure of Brennan et al. to render Applicants' claimed invention obvious. Withdrawal of the rejection is requested.

In summary, Applicants claimed invention is in condition for allowance and Applicants respectfully request a favorable Action upon reconsideration.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date indicated below.

Date: May 3, 1994 Signed: Joanne Stetler
Joanne Stetler